REMARKS

Claims 7-16 are currently pending in this application. Claims 1-6 were cancelled, without prejudice.

Claims 7-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Shaffner (U.S. Patent No. 5,980,573) in view of Fox, Jr. et al. (U.S. Patent No. 5,019,096) and further in view of Nies, et al. (U.S. Patent No. 5,997,544) and Kirschner et al. (U.S. Patent No. 5,942,218).

The Office Action contends that Shaffner describes the use of antibiotic impregnated bone cement comprised of polymethylmethacrylate (PMMA) to prevent the formation and spread of infection (see column 2, lines 4-6, 54, 55). The Office Action alleges that Shaffner teaches the critical clement of incorporating antibiotic agent into PMMA to prevent the spread of infection as in the method of present claim 7; but acknowledges that Shaffner does not name any specific antibiotic or antimicrobial agent for inclusion into the PMMA.

The Office Action alleges that Fox, Jr. et al. teaches that medical devices for external or internal uses are known to introduce bacterial, viral, fungal or other undesirable infection (see column 1, lines 14-16). Fox, Jr. allegedly proposes incorporating antimicrobial agents such as silver salt and chlorhexidine biguanide to produce an infection-resistant medical device (see column 2, lines 24-27, 35-41). The Office Action contends that Fox, Jr. et al. teaches incorporating biguanide into medical devices so that the medical devices would resist bacterial, viral and/or fungal infection. The specific biguanide disclosed by Fox, Jr. et al. is chlorhexidine. At column 14, lines 4-7, Fox, Jr. et al. allegedly discloses that the amount of chlorhexidine acetate can be 0.5 to 3% of the coating.

The Office Action contends that Nies discloses that bone cements containing additives such as antimicrobial agents/antibiotic agents also are known in the art (see column 6, lines 34-39) and the antibiotic agents are used in amounts of 5% to 20% of the monomer weight (see Nies, et al. at column 6, line 49).

The Office Action contends that Kirschner et al. discloses that polyhexamethylene biguanide (PHMBG) is used as a wound antiseptic in amounts of 0.001-0.05% (see the abstract).

The Office Action contends that chlorhexidine and polyhexamethylene biguanide are both biguanides as evidenced by column 6, lines 6 and 7 of Khan et al. (U.S. Patent No. 6,046,143).

The % amount of the biguanide in Kirschner et al. 0.001-0.05 is a narrower range than the amount of active in claims 10, 14 and 15, allegedly meeting the limitations of these claims. With respect to claims 7 and 11, the Office Action contends that one having ordinary skill in the art would select a specific amount of the biguanide that would provide the anticipated resistance to microbial infection. The polyhexamethylene biguanide of Kirschner et al. allegedly meets the limitation of the biguanide of claims 7, 11 and 16. The PMMA bone cement of Shaffner allegedly meets the PMMA of claims 7 and 13-15.

With respect to claim 8, the Office Action contends that since polyhexamethylene biguanide is the recited antimicrobial agent, the limitation of claim 8 allegedly is met when polyhexamethylene biguanide is used. With respect to claims 9 and 13, the Office Action contends that the recitation that PMMA does not adversely affect the wound healing process is a property of PMMA and the PMMA of Shaffner also would not adverse affect the wound healing process and, in fact, Shaffner has not described the PMMA as having adverse effect on wound healing. The prosthesis implant of Shaffner allegedly meets the limitations of claim 12.

The Office Action concludes that one having ordinary skill in the art at the time the invention was made would have incorporated antimicrobial agents such as chlorhexidine and polyhexamethylene biguanide in the PMMA of Shaffner to prevent the formation and spread of infection according to the combined teachings of Shaffner, Fox Jr., Nies and Kirschner et al.. The Office Action further alleges that when using polyhexamethylene biguanide as the antimicrobial agent, one having ordinary skill in the art at the time the invention was made would have been motivated to use the biguanide in amounts of form 0.001 to 0.05% since these amounts have been shown by Kirschner to be effective as an antiseptic.

Applicants respectfully traverse the §103(a) rejection and request that the rejection be reconsidered and withdrawn.

As reiterated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, 82 U.S.P.Q.2d 1385 (2007), the framework for the objective analysis for determining

obviousness under 35 U.S.C. §103 is stated in *Graham v. John Deere*. Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg., No. 195 (October 10, 2007) at page 57527 (hereinafter "Examination Guidelines"). The factual inquiries enunciated by the Court are as follows:

(1) Determining the scope and content of the prior art;

(2) Ascertaining the differences between the claimed invention and the prior art; and

(3) Resolving the level of ordinary skill in the pertinent art.

Examination Guidelines at page 57527.

The Examiner refers in the Office Action to five prior art documents.

Shaffner (U.S. Patent No. 6,245,111 B1) relates to a prosthetic device for placement in an implant area of the body (abstract). This device can be used for temporary replacement of an implanted device to fight and prevent infections (col. 2, lines 42-47). Accordingly, the prosthesis comprises a material like PMMA bone cement which is impregnated with an antibiotic (column 4, lines 41-43).

Fox Jr. et al. (U.S. Patent No. 5,019,096) relates to a method of preparing an infection resistant medical device, wherein the device comprises a coating containing an antimicrobial compound (col. 2, lines 6-21). Preferred coating materials are polyurethane, silicon or degradable polymers. A combination of a silver salt and a biguanide, in particular chlorhexidine, is used as an antimicrobial compound (column 2, lines 22-27).

Nies et al. (U.S. Patent No. 5,997,544) discloses a process and a device for producing sterile-packed bone cement which, amongst other ingredients, may include antibiotics (column 6, lines 34-38).

Kirchner et al. (U.S. Patent No. 5,942,218) relates to an anti-infective material for treatment and/or prophylaxis of wound infections which can comprise amongst others, PHMBG with a mean molecular weight of 2,900 to 15,000 (col. 2, lines 52-57). This substance can be used in form of aqueous solutions, emulsions, suspensions, gels and alike (column 4, lines 6 to 16). The application of PHMBG in bone cement is not disclosed.

In **Khan et al.** (U.S. Patent No. 6,046,143) it is pointed out that chlorhexadine gluconate and polyhexamethylene biguanide belong to the group of biguanides (column 6, lines 6 to 7).

None of the above-cited documents combined as set forth in the Office Action, suggests or discloses the use of polyhexamethylene biguanide in bone cement.

Present claim 7 relates to a method of preventing microbial colonization of a polymethylmethacrylate (PMMA) bone cement surface comprising the step of admixing polyhexamethylene biguanide with the bone cement.

Shaffner and **Nies et al.** describe the possibility of adding certain antibiotics to bone cement. **Fox, Jr. et al.** relates to the use of chlorhexidine but not to the application of polyhexamethylene biguanide as an antiseptic compound. The compound chlorhexidine described in **Fox, Jr. et al.** is a low molecular biguanide derivative with a molecular rate of 505. **Kirchner et al.** relates to a specific high molecular polyhexamethylene biguanide which is however not used in bone cement.

Also a combination of these documents would not provide a method according to present claim 7.

The object of the present invention is to provide polymeric bone cement with an antiseptic compound whereby the antiseptic compound is released by diffusion without the addition of a further additive and which prevents the colonization of the surface of the bone cement with bacteria.

It is known to a person skilled in the art that antibiotic or other compounds can be released from polymeric PMMA based bone cements by matrix diffusion from the cement mass. Different active compounds are thereby characterized by very different release amounts and release kinetics. A determining factor for the release of a compound is obviously its molecular weight, whereby so far a clear relation between the physical-chemical properties of the compound to its releasing properties from PMMA bone cement is not known.

The core of the present invention can be seen in the completely unexpected result of combining PMMA cement and polyhexamethylene biguanide (PHMBG) since compounds with high molecular weights are usually only badly released or practically not released at all due

to their molecular size. In order to achieve the desired antiseptic effect on the cement surface or in the surrounding of the cement, usually relatively small and very good water soluble compound molecules with good diffusion properties through the matrix of the PMMA cement were used. In the case of compounds with a low diffusion rate it had only been possible to increase the added amount of compound or to increase the permeability of the cement matrix by adding further additives or auxiliaries to the cement.

In the present invention, however, it was surprisingly found that very low amounts of high molecular PHMBG suppresses colonization of the cement surface of the bone cement by pathogenic bacteria in an effective manner. This is even more astonishing since PHMBG has inferior prerequisites for release from PMMA bone cement as compared to the usually applied gentamicin (see Figures 1A and lB in the application). Due to the high molecular weight of PHMBG of more than 1700, it was not expected that this substance with a low concentration of up to 1 weight % to the PMMA bone cement would be released in an effective amount during the relatively long time range of more than 7 days.

In the present invention it has been described for the first time that the combination of high molecular PHMBG and PMMA bone cement shows an effective antiseptic effect without further measures. The Applicants assume that the antiseptic effect of PHMBG is not exclusively based on the simple release of the compound into the surrounding media and the destruction of the suspended germs.

In fact, the surprisingly high and long-lasting effectiveness suggests an attachment or colonization of the polymeric cement surface by the released compound so that the compound is enriched on the surface in the form of a thin layer. Similar observations were made in case of adhesion of polyethyleneglycol (PEG) on polymeric surfaces whereby in this circumstance the similarity of PEG and PHMBG in some physical chemical properties has to be pointed out. Subsequently, this yields in the unexpected effect that after incubation in a bacterial culture the colonization of the cement surface is effectively suppressed over a longer time period while the effectiveness of the suspended bacteria in the incubation solution decreases earlier.

Therefore, it was not obvious for a person skilled in the art to conclude from the application of chlorhexidine to the high antiseptic effectiveness of a compound having a different

molecular design as PHMBG when mixing such a low amount to PMMA bone cement. Rather it contradicted the prevailing opinion that small, water soluble molecules are preferred for the release of compounds from solid polymeric carrier materials by matrix diffusion.

Based on this argumentation, it is therefore not obvious for a person skilled in the art to apply the chlorhexidine described by Fox et al. in bone cement according to Schaffner or Nies et al. with the aim of preventing the microbial colonization of the cement surface.

Also the application of the high molecular polyhexamethylenebiguanide described by Kirchner et al. in bone cement was not obvious since it was surprising for a person skilled in the art that polyhexamethylene biguanide is released from bone cement. This effect is not disclosed or obvious from Kirchner et al.

For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants respectfully request consideration of the Information Disclosure Statement submitted herewith and return of an initialed SB-08a form indicating consideration and entry of the references submitted.

Conclusion

It is believed that any pending rejections have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper.

Applicants submit that the pending claims are in condition for allowance, which action is requested. The Examiner is invited to contact the undersigned directly at 412-227-3061 with any questions.

Respectfully submitted,

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